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09/192,167	11/13/1998	THOMAS J. MEADE	A-67412/RFT/	9443

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ROBIN M SILVA
FLEHR HOHBACH TEST ALBRITTON & HERBERT
SUITE 3400 FOUR EMBARCADERO CENTER
SAN FRANCISCO, CA 941114187

EXAMINER

CRANE, LAWRENCE E

ART UNIT

PAPER NUMBER

1623

DATE MAILED: 06/06/2003

25

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/192,167	Applicant(s) Meade et al.	
	Examiner L. E. Crane	Group Art Unit 1623	

- THE MAILING DATE of this communication appears on the cover sheet beneath the correspondence address -

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **--3--** MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be filed after six months from the date of this communication.
- If the prior for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 USC §133).

Status

- ☒ Responsive to communication(s) filed on **-05/23/03 (RCE, amdt D, Declaration & Exhibit)-**.
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- ☒ Claims **---2--4, 6-7, 10 & 16-21---** are pending in the application. Claims **-5, 8-9, 11 & 13-15-** have been cancelled.
- Of the above claim(s) **---[]---** is/are withdrawn from consideration.
- ☐ Claim(s) **---[]---** is/are allowed.
- ☒ Claims **---2-4, 6-7, 10 & 16-21---** are rejected.
- ☐ Claim(s) **---[]---** is/are objected to.
- ☐ Claim(s) **---[]---** are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on **-[]-** are ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on **-[]-** is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119(a)-(d)

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119 (a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.
- ☐ received in Application No. (Series Code/Serial Number) **-[]-**.
- ☐ received in the national stage application from the International Bureau (PCT Rule 17.2(a)).
- * Certified copies not received: **-[]-**.

Attachment(s)

- | | |
|--|---|
| <input type="checkbox"/> Information Disclosure Statement(s), PTO-1449, Paper No(s). -[]- | <input type="checkbox"/> Interview Summary, PTO-413 |
| <input checked="" type="checkbox"/> Notice of Reference(s) Cited, PTO-892 | <input type="checkbox"/> Notice of Informal Patent Application, PTO-152 |
| <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review, PTO-948 | <input type="checkbox"/> Other: -[]- |

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Claims **5, 8-9, 11 and 13-15** have been cancelled, new claims **16-21** have been added, and claims **2-3, 7 and 10** have been amended as per the amendment filed May 22, 2003. Also a Declaration and Exhibits provided by applicant Meade and also filed May 22, 2003 have also been received and made of record. References cited as Exhibits have been separately made of record as citations on the enclosed PTO-892.

Claims **2-4, 6-7, 10 and 16-21** remain in the case.

Examiner notes applicant Meade's declaration and responds generally as follows. Prof. Meade argues that the term "anhydronucleoside" is well understood by the ordinary practitioner as only referring to only certain uridine nucleosides with base-to-sugar linkages from the 2-carbonyl oxygen to a 2'- or 3'- ring carbon of the attached sugar residue. Examiner respectfully disagrees and cites **Goodman** (PTO-892 ref. **UB**) and **Kochetkov et al.** (PTO-892 ref. **VB**) to support the view that the term "anhydronucleosides" (aka cyclonucleosides) is well known in the prior art to encompass a much larger subject matter area than applicant's declaration suggests. Examiner also refers applicant to *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947) which stands for the proposition that "while an applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term." For this reason, and for the numerous reasons found in the rejections below, examiner again respectfully requests applicant to submit claims amended to more "particularly point out and distinctly claim" the instant subject matter with chemical structures in place of functional terminology. It was, and it remains, examiner's considered view that words alone can not adequately establish the metes and bounds (aka property boundaries) of the instant disclosed subject matter.

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The disclosure is objected to because of the following informalities:

Incorporation by reference of essential material by reference to any patent or any publication inserted in the portion of the specification which describes the invention is improper, except for benefit and parent applications. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by applicant, or a practitioner representing applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCAP 1973); *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The attempt to incorporate subject matter into this application by reference to patents and other publications at page 4, line 16; p. 5, lines 4-5; p. 7, lines 15-16; p. 9, lines 11 and 14; p. 10, lines 4-5, 9 and 13; p. 12, lines 10-11; p. 14, lines 9-10 and 23-24; p. 19, lines 7, 9 and 22; p. 21, lines 21-22; and p. 26, lines 7 and 11-12 is improper because it is unclear which part(s) of each patent or publication is essential to the execution of the claimed invention, and because patents and or publications may not be available to the ordinary practitioner seeking to reproduce the instant subject matter if issued and/or subsequent to expiration as prior art.

The specification is replete with grammatical (spelling) errors too numerous to mention specifically. The specification should be revised carefully. Examples of such errors are: misspelling of "hexafluor[o]phosphate" (see newly added experimental procedure, third line from the end), "incorportation," etc.

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Appropriate correction is required.

Claims **2-3, 7, 10 and 16-21** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **2**, the deletion of the term “further comprising” renders said claim lacking in proper antecedent basis because the claim from which it depends does not specify the added subject matter of this claim. The same problem also occurs in claim **3**.

Applicant’s arguments with respect to claims **2 and 3** have been considered but are moot in view of the new grounds of rejection. This new grounds of rejection were necessitated by applicant’s amendment of claims **2 and 3**.

In claim **2**, adding a phosphoramidite moiety to a nucleoside is possible, but how such a group is being added in this case remains unclear because of the lack of definiteness found in claims **7 and 2**.

Applicant’s arguments filed May 23, 2003 have been fully considered but they are not persuasive.

Prof. Meade’s declaration argues that “oligonucleotide synthesis using phosphoramidite chemistry is well established.” Examiner agrees, but notes that applicant’s argument is beside the point made by the rejection above. Examiner notes again that words alone can not adequately define the metes and bounds when a complex multi-step chemical synthesis process is being claimed. Applicant is respectfully requested to amend the independent claims to include complete

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chemical formulas describing the process starting materials, intermediates and products, and to more completely describe in dependent claims how the products of the independent process claims are further modified by additional process steps. Alternatively, this
5 overall result could more directly realized by including all of the process limitations and structural details of reagents, starting materials, intermediates, and products in at least one of the independent claims and further limiting the scope with dependent claims instead of relying on what amounts to a "further comprising," tack on this, tack on that,
10 claim strategy.

Claim 2 provides for the use of an undefined chemical reagent to introduce a "phosphoramidite group" but, since the claim does not set forth any step(s) involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is
15 indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Applicant's arguments filed May 23, 2003 have been fully considered but they are not persuasive.

Applicant is referred to the response to applicant's arguments
20 following the previous rejection. In addition applicant argues separately that "one of ordinary skill would know the steps involved in adding phosphoramidite groups and phosphoramidite-derivatized nucleosides to the terminus of a growing oligonucleotides [SIC] chain." Applicant is correct to a degree (the work of Caruthers et al. and others was
25 patented extensively beginning in the early 1980's), but applicant's response, by its presumption that Caruther's process limitations may be liberally assumed, is merely engaging in hand waving. Examiner finds that applicant's argument continues to ignore the limitations inherent in

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5 claiming processes where there are non-standard substrates and therefore non-standard products. Examiner again respectfully requests claims wherein the ordinary practitioner does not need to guess what the metes and bounds are, and again requests independent claims with complete structural formula for starting materials, intermediates and products.

10 In claim 3, adding a phosphoramidite-derivatized nucleoside to the terminus of a "growing" nucleic acid appears to make reference to the Caruthers process of nucleic acid synthesis, but remains incomplete for failure to specify the structural variables which define the complete chemical structural formula of the "phosphoramidite modified nucleoside."

Applicant's arguments filed May 23, 2003 have been fully considered but they are not persuasive.

15 Applicant is referred to the response following the immediately preceding rejection.

20 Claim 3 provides for the use of a 3'-phosphoramidite derivative of a 2'-modified nucleoside in a process wherein same is incorporated into an oligonucleotide but, since the claim does not set forth any step(s) involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

25 Applicant's arguments filed May 23, 2003 have been fully considered but they are not persuasive.

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Applicant is referred to the response following second rejection identifying claim 3.

5 In claim 7, lines 6-8, the terms "cyclization agent" and "cyclized intermediate" are relatively meaningless unless the details of the chemical reaction being alluded to are provided, thereby rendering this portion of the instant claim lacking in adequately defined metes and bounds.

Applicant's arguments filed May 23, 2003 have been fully considered but they are not persuasive.

10 Applicant Meade's declaration argues that the noted terms would be understood by one of skill in the art in the context of the specification." Examiner respectfully disagrees. The claims define the metes and bounds of the subject matter which applicant seeks to protect. Does applicant intend to protect cyclopurine nucleosides which have a ligand
15 derived substituent and a C-8-to-5'-sugar side chain carbon, base-to-sugar linkage? (See newly cited **Goodman** and **Kochetkov et al.** references) The instant claims read on this subject matter, but the two (2) disclosed examples are limited to uridine analogues, and therefore, by (lack of) definition, fail to describe any purine exemplifications.
20 Therefore, applicant's declaration is apparently arguing against the policy of *Brenner v. Manson* (148 USPQ 689 (S. Ct. 1966)) which stands for the proposition that a patent is granted for subject matter already discovered by an applicant, but is "not a hunting license."

25 In claim 7 the term "an electron transfer moiety" is indefinite functional language which appears to read on a copper wire. Applicant is referred to *Regents of the University of California v. Eli Lilly* (119 F.3d 1559 at 1568; 43 USPQ2d 1398 at 1406 (Fed. Cir 1997)) which MPEP

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§2163 at page 2100-162, column 1, quotes as follows: "A definition by function alone 'does not suffice' to describe a coding sequence 'because it is only an indication of what the gene does, rather than what it is.'"

5 Examiner presumes that this policy extends to entirely functional descriptions of mystery substituents groups attached to mystery nucleosides.

Applicant's arguments with respect to claim 7 have been considered but are moot in view of the new grounds of rejection. This new grounds of rejection were necessitated by applicant's amendment of claim 7.

10 In claim 10 the term "comprising" (**first** and **third** occurrences only) is incorrect in the instant claim because said term implies that the chemical structure of the compound/substituent being claimed contains additional structural component(s) not defined in the claim. Applicant is respectfully requested to substitute narrow language such as --
15 consisting of -- or the like for the noted term.

Applicant's arguments with respect to claim 10 have been considered but are moot in view of the new grounds of rejection. This new grounds of rejection were necessitated by applicant's amendment of claim 10.

20 Claim 10 contains nearly all of the same problems defined above for claim 7. The term "a covalently attached polydentate ligand that chelates a transition metal " only hints at the structure of the intended product. Also said term is inconsistent with other terms in dependent claims 17-21 including "ferrocene" which name separate compounds,
25 not substituents. As a consequence of these technical errors, claims 17-21 all lack proper antecedent basis in claim 10.

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Applicant's arguments with respect to claim 10 have been considered but are moot in view of the new grounds of rejection. This new grounds of rejection were necessitated by applicant's amendment of claim 10.

5 In claim 10, last line, the term "chelates a transition metal" is technically inaccurate because most transition metals do not chelate directly from the metallic state, and those which form chelates in the "zero" oxidation state only do so under special circumstances (e.g. Ni chelates with carbon monoxide). See also in claim 10, last line, the term
10 "adding a transition metal" is also technically incorrect because adding a metal to a chemical compound will usually produce nothing more than a mixture of solid metal and solid chemical compound.

Applicant's arguments with respect to claim 10 have been considered but are moot in view of the new grounds of rejection. This
15 new grounds of rejection were necessitated by applicant's amendment of claim 10.

In claim 10 at lines 2-3, the term "at least one covalently attached polydentate ligand" is incomplete because said term fails to define the locations of attachment or means of attachment (linker?). Said term
20 renders the claim indefinite as to metes and bounds because it fails to include an upper limit on the number of attached ligands.

Applicant's arguments with respect to claim 10 have been considered but are moot in view of the new grounds of rejection. This new grounds of rejection were necessitated by applicant's amendment of
25 claim 10.

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In claim **16** the term "ferrocene" is directed to a compound, not a substituent and therefore said claim lacks proper antecedent basis in independent claim **7**.

5 Applicant's arguments with respect to claims previously in the case have been considered but are moot in view of the new grounds of rejection. This new grounds of rejection were necessitated by applicant's introduction of new claim **16** by amendment.

10 Claim **17** is incomplete because it fails to define the "oxidation state" of the metals listed. Typical chelates of transition metals require that the metal be present in one particular oxidation state.

Applicant's arguments with respect to claims previously in the case have been considered but are moot in view of the new grounds of rejection. This new grounds of rejection were necessitated by applicant's introduction of new claim **17** by amendment.

15 In claim **18** the terms "a donor atom" renders the claim incomplete because the structure of the ligand-substituent has not been completely defined.

20 Applicant's arguments with respect to claims previously in the case have been considered but are moot in view of the new grounds of rejection. This new grounds of rejection were necessitated by applicant's introduction of new claim **18** by amendment.

25 In claims **19-21** the terms "pyridine," "bipyridine," and "phenanthroline" are each directed to a separate chemical compound, not a substituent group, and therefore are both technically incorrect and render the noted claims lacking a proper antecedent basis.

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Applicant's arguments with respect to claims previously in the case have been considered but are moot in view of the new grounds of rejection. This new grounds of rejection were necessitated by applicant's introduction of new claims **19-21** by amendment.

5 Claims **2-11 and 13-15** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

10 In claims **2-11 and 13-15**, the chemical reactants are described using generic terms only, thereby encompassing a substantial area of subject matter for which applicant has failed to provide adequate support within the instant disclosure. Specifically the terms such as
15 "anhydro-nucleoside" (claim **7 and 10**), and "modified nucleoside" (claims **7 and 10**) are directed to a vast array of chemical structures while applicant's specification only discloses a limited number (one) of specific embodiments, leaving the ordinary practitioner the
unreasonable burden of determining which claimed embodiments are actually operative and which are not (undue experimentation) based on
20 what is clearly an inadequate disclosure.

Applicant's arguments with respect to claims **2-11 and 13-15** have been considered but are moot in view of the new grounds of rejection. This new grounds of rejection were necessitated by applicant's amendment of claims **7 and 10**.

25 Applicant's arguments filed May 23, 2003 have been fully considered but they are not persuasive.

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Prof. Meade's declaration argues that the term "anhydronucleoside" (aka "cyclonucleoside") is well understood to "... refer to pyrimidine nucleosides comprising an oxygen bridge between the C-2 of the base pyrimidine and C-2' or C-3' of the ribose" Examiner respectfully
5 disagrees and refers applicant to the newly cited **Goodman** and **Kochetkov et al.** textbook references wherein the definition has considerably more breadth than Prof. Meade asserts. Examiner also recalls that epoxy nucleoside analogues (oxygen bridging the 2' and 3' ribose carbons are also defined as "anhydronucleoside" by some
10 practitioners. Therefore, examiner concludes that applicant's asserted definition is much too narrow in light of the well known disclosures of Goodman and Kochetkov et al., and therefore not a proper basis for defining the scope of a patent claim. This conflict in the scope of defined terms again illustrates the need to amend the noted claims to
15 provide chemical structures to adequately define the scope of terms.

For these reasons, the instant grounds of rejection has been maintained.

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

20 "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a
25 person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made."

Claims 2-4, 6-7, 10 and 16-21 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Nexstar '102** (PTO-892 ref. L).

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The instant claims are directed to a process for making labelled nucleosides from anhydro-nucleosides wherein the label is an "electron transfer moiety," for making the phosphoramidites thereof, and for making standard or modified oligonucleotides or polynucleotides therefrom via phosphoramidite coupling.

The Nexstar '102 reference discloses processes for making labelled nucleosides from anhydro-nucleosides, for making the phosphoramidites thereof, and for making standard or modified oligonucleotides or polynucleotides therefrom via phosphoramidite coupling including compounds modified by metal-ion-containing coordination complexes (see pp. 9-10 and structure 1 at p. 9). Applicant is referred to pages 17, 21, 23, 26, 31, 40, 49, 50 and 53, and claim *1*, at p. 59, lines 10-11, and claims *5*, *20*, *22* and *25* wherein the last three claims disclose the nucleoside starting material, disclose the phosphoramidite analogues of the nucleoside, and imply the use of said phosphoramidites to make oligonucleotides incorporating the modified nucleosides by claiming compounds which could be the product of a phosphoramidite oligonucleotide synthesis.

Teachings of the prior art which disclose in detail subject matter which reads on the invention as claimed is deemed to render the instant claims lacking in patentable distinction in view of the noted prior art.

Therefore, the instant claimed process for making labelled nucleosides from anhydro-nucleosides, for making the phosphoramidites thereof, and for making standard or modified oligonucleotides or polynucleotides therefrom via phosphoramidite coupling, would have been obvious to one of ordinary skill in the art

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having the above cited reference before him at the time the invention was made.

Applicant's arguments filed May 23, 2003 have been fully considered but they are not persuasive.

5 Applicant argues that the instant invention is a "modified nucleoside comprising an electron transfer moiety and at least one polydentate ligand." Examiner is unclear that applicant understands that the last two structures of the process illustrated in Figure 3 have a single substituent which is a metal chelate, and that when the last molecule of Figure 3 has
10 been incorporated into a suitably substituted oligonucleoside, said incorporation apparently renders the extended oligonucleotide capable of acting as an electron transfer agent.

In addition, examiner disagrees with applicant's conclusory statements concerning the applicability of the Nextar '102 reference.
15 Examiner has maintained the instant rejection because applicant has insisted on not incorporating the structures of starting materials, intermediates and final products in the claims. While examiner agrees that Nextar 102's disclosure does not correspond to the instant disclosure, examiner insists that the breadth of the instant claims
20 courtesy of their reliance on entirely functional terminology to describe the chemical actors in the process means that one of ordinary skill can still find an overlap of the instant claims with a broad reading of the Nextar '102 reference.

This is an RCE of applicant's earlier application S.N. **09/192,167**.
25 All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds or art of record in the next Office action if they had been entered in the earlier

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application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

5 A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL
ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS
ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS
OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY
ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH
10 SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY
PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND
ANY EXTENSION FEE PURSUANT TO 37 C.F.R. §1.136(a) WILL BE
CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO
EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN
SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

15 Papers related to this application may be submitted to Group 1600
via facsimile transmission(FAX). The transmission of such papers must
conform with the notice published in the Official Gazette (1096 OG 30,
November 15, 1989). The telephone numbers for the FAX machines
operated by Group 1600 are **(703) 308-4556** and **703-305-3592**.

20 Any inquiry concerning this communication or earlier
communications from the examiner should be directed to Examiner L. E.
Crane whose telephone number is **703-308-4639**. The examiner can
normally be reached between 9:30 AM and 5:00 PM, Monday through
Friday.

25 If attempts to reach the examiner by telephone are unsuccessful, the
examiner's supervisor, Mr. James O. Wilson, can be reached at (703)-
308-4624.

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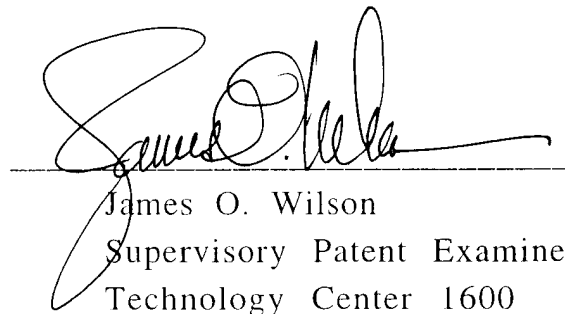
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Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **703-308-1235**.

LECrane:lec

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06/04/03



James O. Wilson
Supervisory Patent Examiner
Technology Center 1600